Seroprevalence of SARS-CoV-2 (COVID-19) among Healthcare Workers in Saudi Arabia: Comparing Case and Control Hospitals

Haleema Ali Alserehi[1*], Ada Mohammed Alqunaibet[1], Jaffar A. Al-Tawfiq[2,3,4*], Naif Khalaf Alharbi[5,6], Abeer Nizar Alshukairi[7], Khalid Hamdan Alanazi[8], Ghada Mohammed Bin Saleh[8], Amer Mohammed Alshehri[9], Abdulrahman Almasoud[5], Anwar M. Hashem[10,11], Amaal Rabie Alruwaily[1], Rehab Habeeb Alaswad[1], Hind Mohammed Al-Mutlaq[1], Abdulllah Ali Almudaiheem[1], Fatmah Mahmoud Othman[12], Sumyah Abdullah Aldakeel[9] , Mouath Rashid Abu Ghararah[9] ,Hani Abdulaziz Jokhdar[13], Abdullah Rshoud Algwizani[14], Sami Saeed Almudarra[1], Ahmed Mohammed Albarrag[9,15]

[1]Executive Department of Global Health, Epidemiology, surveillance and preparedness affairs, Executive Department of Research, Saudi Center for Disease Prevention and Control, Riyadh, Saudi Arabia; [2]Infectious Disease Unit, Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, [3]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [4]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [5]Vaccine Development Unit, Department of Infectious Disease Research, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [6]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia [7]Department of medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia; [8]Infection and Control Department, Ministry of Health, Riyadh, Saudi Arabia; [9]Public Health Lab, Saudi Center for Disease Prevention and Control, Riyadh, Saudi Arabia; [10] Department of Medical Microbiology and Parasitology, Faculty of Medicine,

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King Abdulaziz University, Jeddah, Saudi Arabia;[11]Vaccines and Immunotherapy Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [12]Research department, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [13]Public Health, Ministry of Health, Riyadh, Saudi Arabia; [14]Saudi Cenetr for Disease Control and Prevention, Riyadh, Saudi Arabia; [15]Department of Pathology, School of Medicine, King Saud University, Riyadh, Saudi Arabia

Correspondence:

Dr. Haleema Ali Alserehi*

[1]Executive Department of Global Health,Saudi Center for Disease Prevention and Control, Riyadh, Saudi Arabia

E-mail: dr_al_serihi@hotmail.com, halserehi@moh.gov.sa

AND

Dr. Jaffar A. Al-Tawfiq*

Johns Hopkins Aramco Healthcare, Dhahran 31311, Saudi Arabia.

E-mail address: jaffar.tawfiq@jhah.com; jaltawfi@yahoo.com

Tel: +966-13-870-3524; Fax: +966-13-870-3790

Abstract:

Background: Healthcare workers (HCWs) stand at the frontline for fighting coronavirus disease 2019 (COVID-19) pandemic. This puts them at higher risk of acquiring the infection than other individuals in the community. Defining immunity status among health care workers is therefore of interest since it helps to mitigate the exposure risk.

Study Design: Eighty-five hospitals across KSA were divided into two groups: COVID-19 referral hospitals are those to which RT-PCR-confirmed COVID-19 patients were admitted or referred for management (Case-hospitals). COVID-19 non-affected hospitals where no COVID-19 patients had been admitted or managed and no HCW outbreak (Control hospitals). Next, seroprevalence of SARS-CoV-2 among healthcare workers (HCWs) was evaluated; there were 12,621 HCWs from the 85 hospitals.

Result: There were 61 case-hospitals with 9,379 (74.3%) observations, and 24 control-hospitals with 3,242 (25.7%) observations. The overall positivity rate by the immunoassay was 299 (2.36%) with a significant difference between the case-hospital (2.9%) and the control-group (0.8%) (P value <0.001). There was a wide variation in the positivity rate between regions/cities in Saudi Arabia, ranging from 0% to 6.31%. Of the serology positive samples, 100 samples were further tested using the SAS2pp neutralisation assay; 92 (92%) samples showed neutralisation activity.

Conclusion: The seropositivity rate in KSA is low and varies across different regions with higher positivity in case-hospitals than control-hospitals. The lack of NAb in 8% of the tested samples could mean that assay is a more sensitive assay or that neutralisation assay has a lower detection limits; or possibly that some samples had cross-reaction to spike protein of other coronaviruses in the assay, but these were not specific to neutralize SARS-CoV-2.

Introduction:

Healthcare workers (HCWs) stand at the frontline for fighting coronavirus disease 2019 (COVID-19) pandemic. This puts them at higher risk of acquiring the infection than other individuals in the community (Ferioli et al. 2020). Several hospitals, since the beginning of this pandemic, have implemented strategies to protect their healthcare workers that

include, but not limited to, providing adequate personal protective equipment, weekly shifts system, period screening of their staff, and other IPC measures (Al-Tawfiq et al. 2020; Barranco and Ventura 2020; Galan et al. 2020). Since the global emergence of this pandemic, in March 2020, many health care settings have started to report the burden of COVID-19 infection among their healthcare workers (Barranco and Ventura 2020; Folgueira et al. 2020; Wei et al. 2020). However, reporting only symptomatic and infected cases among HCWs could lead to a significant underestimation of the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Thus, many reports indicate the presence of subclinical infection among healthcare workers, which impose threaten risk to other patients, co-workers, and families (Ferioli et al. 2020; Korth et al. 2020a). Defining immunity status among health care workers, therefore, is of interest since it helps to mitigate the exposure risk.

The evidence on COVID-19 infection among healthcare workers is growing in which several studies have estimated the seroprevalence of SARS-CoV-2 among their healthcare workers. The results of those studies indicate that between 1.7 to 11% of healthcare workers were seropositive (Brandstetter et al. 2020; Folgueira et al. 2020; Galan et al. 2020; Garcia-Basteiro and Gemma Moncunill, Marta Tortajada, Marta Vidal, Caterina Guinovart, Alfons Jimenez, Rebeca Santano, Sergi Sanz, Susana Mendez, Anna Llupia, Rugh Aguilar, Selena Alonso, Diana Barrios, Carlo Carolis, Pau Cistero, Eugenia Choliz, A 2020; Paderno et al. 2020a). Importantly, a number of those studies reported the occurrence of seropositivity among individuals who did not report any symptoms by 38-48% (Folgueira et al. 2020; Galan et al. 2020; Garcia-Basteiro and Gemma Moncunill, Marta Tortajada, Marta Vidal, Caterina Guinovart, Alfons Jimenez, Rebeca Santano, Sergi Sanz, Susana Mendez, Anna Llupia, Rugh Aguilar, Selena Alonso, Diana Barrios, Carlo Carolis, Pau Cistero, Eugenia Choliz, A 2020). The

advantages of seroprevalence studies rely on the usefulness of such a method to assess the level of subclinical exposure among cases and identify high-risk groups (Al-Tawfiq and Memish 2020). The aim of the study was to evaluate seroprevalence of SARS-CoV-2 antibodies among HCW in various hospitals in the Kingdom of Saudi Arabia (KSA) and to compare seroprevalence between HCWs in hospitals caring for COVID-19 cases and other hospitals.

Materials and Methods:

Study Population: The study included hospitals with more than 200 beds. Study hospitals were divided into two groups: COVID-19 referral /affected hospitals are those to which RT-PCR-confirmed COVID-19 patients were admitted or referred for management (Case-hospitals). COVID-19 non-affected hospitals where no COVID-19 patients had been admitted or managed and no HCW outbreak (Control hospitals). We aimed to include 12000 HCWs with a Case Control ratio of 2:1. HCWs who agreed to participate signed consents for participation. Health workers included physicians, nurses, pharmacists, respiratory therapists, and administrative support who agree to participate in the study. The HCWs were from departments at high risk to get exposed to COVID 19 cases: medicine, intensive care units and emergency departments. We excluded HCWs who were experiencing any symptoms of COVID-19 at the time of enrolment.

Specimens were transported to the Saudi CDC Lab. Samples were transported and delivered within 48 hr at 4-8^{0}C. When serum samples were not processed immediately, sera were stored at -80°C. Serological testing: Serum samples were screened for the presence of SARS-CoV-2 antibodies using a chemiluminescent microparticle immunoassay (CMIA) which

detects IgG raised against the nucleocapsid protein of SARS-CoV-2. (Abbott Architect SARS-CoV-2 IgG kit, Abbott, USA).

SARS-CoV-2 pseudotyped viral particles (SARS2pp) neutralisation assay: SARS-CoV-2 pseudotyped viral particles (SARS2pp) were produced in HEK293T cells and titrated using Huh7.5 cells as described for MERSpp previously (Grehan et al. 2015; Alharbi et al. 2019; Almasaud et al. 2020). Here, 100 samples that were positive by immunoassay (one third of the positive samples) were prepared in a 1:20 and 1:40 dilutions to assess their neutralisation activity (percent). In addition, 20 of these 100 samples were prepared in eight serial dilutions (3-fold) starting from 1:20, and tested for nAbs titre in duplicates.

A standard concentration of SARS2pp (equivalent to 200,000 RLU) and Huh7.5 cells (10,000 cells) were added to each well of 96-well opaque plate. Cells only and cells-plus-SARS2pp only (both without serum) were included in quadruplicate as controls to determine 0% and 100% neutralisation activity, respectively. Following 48 h incubation, cells were lysed and the assay was developed using Bright-Glo™ Luciferase Assay System (Promega, USA) and luciferase activity was measured using a luminometer. Samples were considered positive if neutralisation activity was detected in both dilutions (1:20 and 1:40) and the neutralisation percent was reported as compared to cell-plus-SARS2pp control. For 20 samples, a further evaluation of the NAb titres (IC50 neutralisation titres) were calculated for each serum sample across 8 dilutions and plotted using GraphPad Prism.

The study was approved by the Saudi Ministry of health IRB (H-01-R-009).

Statistical Method:

Our descriptive analysis included counts and proportions for categorical variables. For bivariable analysis, the Chi-square test was conducted to assess the association between

Serology test and Case-control hospitals. Another Chi-square test was conducted to assess the association between regions and the serology test. We employed logistic regression models to examine the relationship between the outcome Serology test and the exposure Case-control hospitals, and the relationship between the outcome serology test and the exposure Regions. The magnitude of association presented as the odds. All reported 95% CI and P-values in the two models were based on the logistic regression. We used STATA 15.1 to perform all of the analysis. The significance level for all of the statistical tests was set at 0.05.

Results:

During the study period, there were 12,621 HCWs from 85 hospitals. There were 61 case-hospitals with 9,379 (74.3%) HCWs, and 24 control-hospitals with 3,242 (25.7%) HCWs. The overall positivity rate by immunoassay was 299 (2.36%) of the total 12621 HCWs. Out of the 299 seropositive HCWs, 86 (28.7%) were positive by PCR for SARS-CoV-2. However, none was symptomatic as we excluded symptomatic HCWs from the study. There was a significant difference in the positivity rate between case-hospitals (2.9%) and the control-hospitals (0.8%) with a crude Odd Ratio of 3.71 (95% CI; 2.47-5.55) (P value <0.001). There was a wide variation in the positivity rate between regions/cities in Saudi Arabia from 0% to 6.31% (Table 2). The highest rate of positivity was in Makkah (6.31%, OR 6.3) and Al-Madinah Al-Mounawarah (4.55%, OR 4.46); followed by the Eastern Region (1.55%, OR 1.47), Aseer (2.18%, OR 2.08). The crude Odd Ratio based on Riyadh (1.06% positivity rate) is also shown.

To confirm that the immunoassay test is reliable in detecting anti-SARS-CoV-2 IgG antibodies, 100 seropositive samples (1/3 of the total positive samples) were randomly

selected for further testing using the SAS2pp neutralisation assay. Of these samples, 92 (92%) samples showed neutralisation activity; 76 of which had higher than 50% neutralisation at 1:40 dilution (Figure 1). Additionally, 20 of the 100 samples were further evaluated to report the IC50 NAb titres (Figure 2). Some of these sera did not show NAb indicating that they could have a low level of NAb that could not be determined by the SAS2pp neutralisation assay or that these samples have antibodies against related coronaviruses and might have cross-reacted with the spike antigen in immunoassay.

Discussion:

COVID-19 is an emerging disease caused by the SARS-CoV-2 and was declared as a pandemic in March 2020. The first case of COVID-19 was reported in Saudi Arabia on March 2nd, 2020 and the current study was conducted between May 20th and 30th, 2020 at the times when the Kingdom of Saudi Arabia had 62,000-80,000 cases. The study was conducted just before the peak of cases in the country. Being front liners in the control of the disease, HCWs represent 3.5% to 16% of all cases in China and USA respectively (Europenan Center for Disease Control and Prevention). Previously, there were several MERS-CoV hospital outbreaks described in KSA (Al-Tawfiq and Auwaerter 2019). The most important sero-epidemiological study among HCW has shown that 20 out of 250 cases were diagnosed by serology with various attack rate between various departments based on extent of exposure to MERS (Alraddadi et al. 2016) and only 25% of cases had positive PCR. There is one report describing the seroprevalence of MERS-CoV among HCWs during the Korean outbreak with a seropositivity of 0.7% in HCW who did not use personal protective equipment (PPE) and 0% in those who used PPE (Kim et al. 2016). With the ongoing outbreak and concern of asymptomatic transmission, several asymptomatic HCWs can

infect patients in addition several asymptomatic patients can infect HCW. With the increasing number of HCWs that are isolated at home following exposure to COVID-19 cases and with the increasing number of COVID-19 patients requiring more care from HCWs, better strategies were suggested to assess the immunity of HCWs to protect both patients and HCWs; especially that the COVID-19 PCR testing may have detection limitations.

At the national level, studying the prevalence of SARs-CoV-2 among Saudi healthcare workers is important to understand the exposure risk among this population, and to compare different risk factors of the infection, which can influence infection control measures and policies. Our aim was to study the seroprevalence of COVID-19 among HCW in various hospitals in KSA using a screening serological tests followed by a confirmatory neutralization test. However, it may be important to note that screening serological tests are lacking specificity as advised by the WHO.

In this study the overall rate of positive serology was 2.3% among HCWs. In a study in Tennessee, USA, of 249 front-line HCWs who cared for COVID-19 patients, 8% tested positive for COVID-19 antibodies by serology (Stubblefield et al. 2020a). In a study of 2507 HCWs in Italy, the positivity rate was 0% for IgM and 0.7% for IgG antibodies (Lahner et al. 2020). We observed a higher positivity rate among case-hospitals of 2.9% vs 0.8% in the control hospitals. Thus, the overall rate of IgG positivity in this study is 3.3 times that seen in the study from Italy. However, there is a variable rate of positivity among HCWs worldwide(Barrett et al. 2020; Brandstetter et al. 2020; Folgueira et al. 2020; Galan et al. 2020; Garcia-Basteiro and Gemma Moncunill, Marta Tortajada, Marta Vidal, Caterina Guinovart, Alfons Jimenez, Rebeca Santano, Sergi Sanz, Susana Mendez, Anna Llupia, Rugh Aguilar, Selena Alonso, Diana Barrios, Carlo Carolis, Pau Cistero, Eugenia Choliz, A 2020;

Hains et al. 2020; Korth et al. 2020a; Paderno et al. 2020b; Sandri et al. 2020). Antibody response may be related to the level of exposure in hospitals as exemplified by the differences in the control-hospitals versus the case-hospitals in this study. In an Infectious Diseases specialized setting in Naples, Southern Italy, antibody seroprevalence was 1.7% among tested HCWs (Fusco et al. 2020), indicating low rate despite the possible high exposure. Therefore, additional explanations is required; and this might be because of the short-lived antibody response or the timing of the antibody tests post exposure (Seow et al. 2020).

The study showed variable seroprevalence in different regions. Case-hospitals were also more likely to have positive serology compared to the control-hospitals. Although most of the control hospitals were in the regions where the number of cases is low, control hospitals from regions with higher community cases were also included. Multiple factors may play a role in the occurrence of higher seroprevalence among the HCW in the case-hospitals at different regions. One factor is of course the number of COVID-19 cases in these hospitals. Another factor is the number of COVID-19 cases in the community. As indicated above, this study was conducted between May 20th and 30th, 2020 at the time when the Kingdom had 62,000-80,000 cases. And there were different positivity rates and cases between the different regions at that time. Of the total reported cases at that time, Makkah region accounted for 41% of all the reported cases indicating a higher prevalence of cases in the region. In addition, 15% of the cases were in Madinah, 20% in Riyadh, 19% in the eastern region and less than 2% in other regions. There was a high number of community cases in the regions that have high HCW seroprevalence for COVID-19 such as what was seen in Makkah and Madinah compared to Riyadh and Eastern region. There were relatively high number of community cases in Riyadh and Eastern province but these

showed low HCW seroprevelance. The findings suggest that the high seroprevalence may be secondary to community exposure although other factors cannot be excluded such hospital environment and compliance with infection control measures. One study showed that HCW positivity for SARS-CoV-2 was associated with working in COVID-19 units, (RR = 2.449, confidence interval = 1.062-5.649, P= .027), a positive household, inappropriate use of PPE, having a break in the same personnel break room as an HCW without a medical mask for more than 15 minutes, consuming food within 1 m of an HCW, and non-compliance with safe social distancing (Çelebi et al. 2020). It was found that exposure of HCWs to SARS-CoV-2 may be in the hospital, from household members, or community-acquired (Burrer et al. 2020). In one study, 137 (27%) of 500 HCW were positive for SARS-CoV-2 antibody with much higher rate among symptomatic participants (75%) and of all the positive HCWs 34% had community exposure (Venugopal et al. 2020). Seroprevalence is also related to the level of HCWs exposure and one study showed that seroprevalence was higher in an intermediate-risk-group vs. high-risk-group (5.4 % vs. 1.2 %) (Korth et al. 2020b). Another study showed that enzyme immunoassay (EIA) and microneutralization assay were positive in 17.14% (18/105) of HCWs who were contacts of COVID-19 patients despite negative SARS-CoV-2 (Chen et al. 2020). The risk of seropositivity was lower with wearing face mask (odds ratio [OR], 0.127, 95% confidence interval [CI] 0.017, 0.968) (Chen et al. 2020). We showed that HCWs working in case-hospitals had higher positivity rate and this was similar to a study that showed 19 (7.6%) of 249 HCWs who worked in COVID-19 units for one month were positive (Stubblefield et al. 2020b). However, in another study of 202 HCWs the positivity rate was 14.4% for IgM and 7.4% for IgG with no relationship to COVID-19 exposure (Sotgiu et al. 2020). It was interesting to note that one study showed similar seropositivity among HCWs with heavy and low COVID-19 exposure (Hunter et al. 2020).

Thus, a multi-centre study is needed to elucidate carefully factors contributing to the seropositivity of HCWs to SARS-CoV-2. Such identification would aid in better understanding and facilitate the introduction of preventive measures for HCWs.

The lack of NAb in 8% of the tested samples could mean that assay is a more sensitive or that neutralisation assay has a lower detection limit. It could possibly be that some sera had cross-reactive antibodies to the spike protein in the serological assay originating from an exposure to other coronaviruses; especially that MERS is endemic in Saudi Arabia and the asymptomatic rate of MERS infections in understudied. The ELISA or CMIA assays are not 100% specific and positive reactions were obtained for subjects with antibodies against other coronaviruses. The assay used is a chemiluminescent microparticle immunoassay (CMIA) with higher specificity compare to ELISA. The specificity of the assay based on the available studies is 99.2 -100% (Bryan et al. 2020; Perkmann et al. 2020; Public Health England 2020). The tested samples without Nab activities is more likely to have lower level of antibody titre to be detected by Nab assay or that these samples have antibodies against related coronaviruses and might have cross-reacted with the spike antigen in immunoassay.

This study is the first seroprevalence of HCWs in Saudi Arabia. Few weaknesses are possible. The hospitals were classified based on the available national surveillance data (National Health electronic surveillance system). The control hospitals implemented the same criteria and indication for COVID-19 testing as the case hospitals. Indications for repeating the test were similar in both groups of hospital. Control Hospitals were defined as COVID-19 non-affected hospitals as there was no management of COVID-19 patients and

there were no COVID-19 outbreaks among HCWs. And thus we could not exclude completely the diagnosis of a single COVID-19 case in the control hospital.

In conclusion, this is a national serosurvey of SARS-CoV-2 among HCWs working in hospitals with and without COVID-19 patients. The study was based on a random sample of HCWs. Since the duration of detectable antibodies is variable no recommendation can be generated for those who have negative SARS-COV2 antibodies. The findings may indicate a large number of HCWs are still at high risk of acquiring infection in different setting and thus strong strategies are need to strengthen infection control measures, and to continue to have staff training. We included

Authors statement

Haleema Alserehi: Conceptualization, Design and Methodology Validation, Analysis, data/evidence collection, Resources, Data Curation, Writing Original Draft, Supervision; Ada Mohammed Alqunaibet: Conceptualization, Design and Methodology Validation, Analysis, Data Curation, Writing - Original Draft; Jaffar A. Al-Tawfiq: Analysis, Writing - Original Draft, Writing - Review & Editing; Naif Khalaf Alharbi: Analysis, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing; Abeer Nizar Alshukairi: Conceptualization, Design and Methodology, Validation; Khalid Hamdan Alanazi: Conceptualization, data/evidence collection, Resources, Data Curation; Ghada Mohammed Bin Saleh: Analysis, data/evidence collection, Resources, Data Curation; Amer Mohammed Alshehri: Analysis, data/evidence collection, Resources, Data Curation; Abdulrahman Almasoud: Analysis, Resources, Data Curation; Anwar M. Hashem: Analysis, Resources, Data Curation; Amaal Rabie Alruwaily: data/evidence collection, Resources, Data Curation, Writing - Original Draft; Rehab Habeeb Alaswad: data/evidence collection, Data Curation; Hind Mohammed Al-Mutlaq: data/evidence collection, Data Curation; Abdulllah Ali Almudaiheem: data/evidence collection, Resources, Data Curation; Fatmah Mahmoud Othman: data/evidence collection, Resources, Writing - Original Draft; Sumyah Abdullah Aldakeel: Analysis, Resources; Mouath Rashid Abu Ghararah: Analysis, Resources; Hani Abdulaziz Jokhdar: Conceptualization, Design and Methodology, Resources; Abdullah Rshoud Algwizani: Conceptualization, Design and Methodology, Resources; Sami Saeed Almudarra: Conceptualization, Design and Methodology, Design and Methodology, Writing - Review & Editing, Supervision; Ahmed Mohammed Albarrag: Conceptualization, Design and Methodology, Analysis, Resources, Writing - Review & Editing.

All authors approved the final manuscript

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Tables and Figures:

Table 1: Rate of Positive serological assay between Control-group and Case-hospital among Healthcare Workers.

	Total	Positive	Percent positive
Control	**3,242**	**26**	**0.8**
Case	**9,379**	**273**	**2.9**
Total	**12,621**	**299**	**2.36**
	Pearson chi2(1) = 44.2698 P = 0.0001		

Table 2: Percentage of positivity rate among Healthcare Workers in relation to the Region/City in Saudi Arabia

Regions	**Positive**	**Percent**	**Total**	**Crude OR (95% CI)**	**(95% CI)**		**P-Value**
Hail	1	0.2	**501**	0.18	0.02	1.36	0.099
Najran	1	0.23	**437**	0.21	0.02	1.56	0.13
Baha	1	0.34	**296**	0.31	0.04	2.32	0.258
Qassim	2	0.39	**513**	0.36	0.08	1.52	0.168
Northern Border	1	0.65	**154**	0.61	0.08	4.49	0.629
Jazan	3	0.67	**447**	0.63	0.19	2.06	0.447
Riyadh	36	1.06	**3,405**	1			
Eastern Region	29	1.55	**1,869**	1.47	0.9	2.41	0.122
Aseer	19	2.18	**870**	2.08	1.19	3.66	0.01
Madinah	37	4.55	**813**	4.46	2.8	7.1	<0.001
Makkah	169	6.31	**2,678**	6.3	4.38	9.06	<0.001

Total	**299**	**2.37**	**12,621**				

Figure 1: Neutralisation assay (NA) was performed based on SARS-CoV-2 pseudotyped viral particles (SARS2pp).

A: Neutralisation percentage of serum samples (n=100) that were diluted 1:40 and run in SARS2pp NA. Dotted line shows 50% neutralisation activity. **B:** Some serum samples (n=20) were further tested in SARS2pp NA in a 3-fold serial dilution to present the titre nAb as 50% inhibitory concentration (IC50).